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09/225,426	01/05/1999	JOHN P.N. ROSAZZA	P00297US1	2480

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HEIDI S NEBEL  
ZARLEY MCKEE THOMTE VOORHEES & SEASE  
801 GRAND AVENUE, SUITE 3200  
DES MOINES, IA 503092721

EXAMINER

SAUCIER, SANDRA E

ART UNIT

PAPER NUMBER

1651

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18

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No. 09/225,426	Applicant(s) Rosazza et al.
Examiner Sandra Saucier	Art Unit 1651

— The MAILING DATE of this communication appears on the cover sheet with the corresponding address —

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

1)  Responsive to communication(s) filed on Oct 23, 2001

2a)  This action is FINAL. 2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle* 1035 C.D. 11; 453 O.G. 213.

4)  Claim(s) 1, 3, 5, 6, 9-11, 13, 15, and 16 is/are pending in the application.

4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 1, 3, 5, 6, 9-11, 13, 15, and 16 is/are rejected.

7)  Claim(s) \_\_\_\_\_ is/are objected to.

8)  Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

11)  The proposed drawing correction filed on \_\_\_\_\_ is: a)  approved b)  disapproved.

12)  The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. § 119

13)  Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)  All b)  Some\* c)  None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

### Attachment(s)

15)  Notice of References Cited (PTO-892) 18)  Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_

16)  Notice of Draftsperson's Patent Drawing Review (PTO-948) 19)  Notice of Informal Patent Application (PTO-152)

17)  Information Disclosure Statement(s) (PTO-1449) Paper No(s). 17 20)  Other: \_\_\_\_\_

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#### DETAILED ACTION

Claims 1, 3, 5, 6, 9-11, 13, 15, and 16 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### *Continued Prosecution Application*

The request filed on 10/23/2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/225426 is acceptable and a CPA has been established. An action on the CPA follows.

The claims are examined to the extent that they read on peptides as elected in paper # 9. As art has been applied on the elected embodiment "peptides", search and art for other embodiments, such as L-arginine or polyarginine has not been applied since they are clearly not peptides. See MPEP 809.02 for examination with regard to election of species.

#### *Claim Rejections - 35 USC § 112*

##### INDEFINITE

Claims 1, 5, 6, 9-11 and 15 remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specification has differing meanings for the term "peptide". On page 9, it reads "peptide is arbitrarily defined as a peptide chain having a single peptide bond". However, on pages 15 and 16, Table 1 and other places, peptide is used in its usual sense to mean a few amino acids linked with peptide bonds, such that bradykinin or a five amino acid sequence is called a peptide. The use of the term "peptide" is contradictory throughout the specification and the claims which leads to confusion as to the scope of the claims. Under one usage, no peptides are present in the independent claims, under another usage BK and its derivatives are peptides. Both contradictory usages appear to be supported by the specification. Applicant has still not clarified this issue. The issue would be moot if applicant canceled the claims directed only to "peptide" such as claim 1. Claim 3, which has specific peptides, is definite since the peptides are defined.

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The term "peptide" is not usually restricted to mean a dipeptide to one of skill in the art. Thus, the term "peptide" due to confusion in the specification, has been interpreted to have its usual meaning, that is a few amino acids linked by peptide bonds, in the interest of compact prosecution. Thus, BK and the compounds identified by SEQ ID numbers have been considered to be peptides for prosecution.

*Claim Rejections – 35 USC § 102*

Claims 1, 5, 6, 10, 11, 15 and 16 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by Groves *et al.* [V].

The claims are directed to a one step method of intravenously administering from 20–500 µg/kg of a peptide, oligopeptide or protein or L-arginine, containing an arginine available to NOS, to a mammal in order to regulate NO production.

(The claims are examined to the extent that they read on peptides.)

Groves *et al.* disclose the one-step method of the intravenous administration of a regulator of NO production, HOE-140, a bradykinin B2 receptor antagonist to a human. This reference fulfills the one step method of administering a NO-regulating amount of an peptide. Bradykinin, an arginine containing peptide, stimulates the production of NO and vasodilation, while the peptide, HOE-140, which is a known bradykinin antagonist which contains arginine, limits NO production. The dosage is 200µg/min for 15mins. If one assumes that the average weight of a patient is 180 lbs, this is a dosage of about 36µg/kg, which is well within applicants' claimed range.

*Response to Arguments*

Applicants argue that Groves *et al.* teach that the administration of HOE-140 has no effect on NO on page 3429 of the reference. The reference states that "The fact that HOE-140 had no influence on NO synthase activity in cultured endothelial cells implies that its effects (*in vivo*) were not attributable to A NONSPECIFIC INHIBITION of enzymatic NO formation." Parenthetical insertion is mine. However, the effect of HOE-140 *in vivo* may have been as SPECIFIC inhibitor of NO formation. Please see page 3429, first paragraph where it is stated, "The vasodilatory actions of bradykinin are mediated largely through the stimulated release of NO,...and it is therefore likely that the

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actions of HOE 140 were to reduce the endogenous bradykinin stimulated release of one or more of these endothelium derived vasodilators. In other words, the authors think that it is likely that HOE 140 is a bradykinin antagonist, which antagonists are suggested in the specification as NOS modulators.

Applicants continue to argue that their method requires the stimulation or inhibition of NO synthetase. However, their method is a one step method of administering to a mammal for prevention or treatment of certain nitric oxide-mediated pathogenic conditions. Applicants appear to argue that the administration of HOE 140, a known bradykinin B<sub>2</sub> receptor agonist, does not modulate NO synthetase. The reference only states that NO synthetase is not modulated in cultured endothelial cells, not in an intact mammal as the present claims are directed.

In any case, the one step method of the claims is the same as the one step method of administering taught by the reference. The subject of the reference is the same as the subject of the claims, and all mammals are in need of prevention of disease. The dosage of the reference falls within the range of the dosage of the claims. The compound of the reference, HOE-140, is a peptide which contains at least one arginine at a terminus of the peptide. Thus, it is reasonable to conclude that the result of treating the same patient with a compound which falls within the definition of the claims and in within the same dosage of the claims would have the same effect as claimed.

Applicants continue to argue that if the reference does not directly teach their explicit effect as a consequence of their one step method of administrating, it is not anticipatory. This is not correct because the effect is a direct consequence and flows from the step of administering.

"To invalidate a patent by anticipation, a prior art reference normally needs to disclose each and every limitation of the claim. See Standard Havens Prods., Inc. v. Gencor Indus., Inc., 953 F.2d 1360, 1369, 21 USPQ2d 1321, 1328 (Fed. Cir. 1991). However, a prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it. See *id.*; *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 630, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Under the principles of inherency, if the prior art necessarily functions in accordance with, or

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includes, the claimed limitations, it anticipates. See *In re King*, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. See *Titanium Metals*, 778 F.2d at 780. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. See id. at 782. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. See id. at 782 ("Congress has not seen fit to permit the patenting of an old [composition], known to others . . . , by one who has discovered its . . . useful properties."); *Verdegaal Bros.*, 814 F.2d at 633.

This court's decision in *Titanium Metals* illustrates these principles. See *Titanium Metals*, 778 F.2d at 775. In *Titanium Metals*, the patent applicants sought a patent for a titanium alloy containing various ranges of nickel, molybdenum, iron, and titanium. The claims also required that the alloy be "characterized by good corrosion resistance in hot brine environments." *Titanium Metals*, 778 F.2d at 776. A prior art reference disclosed a titanium alloy falling within the claimed ranges, but did not disclose any corrosion-resistant properties. This court affirmed a decision of the PTO Board of Appeals finding the claimed invention unpatentable as anticipated. This court concluded that the claimed alloy was not novel, noting that "it is immaterial, on the issue of their novelty, what inherent properties the alloys have or whether these applicants discovered certain inherent properties." Id. at 782. This same reasoning holds true when it is not a property, but an ingredient, which is inherently contained in the prior art. The public remains free to make, use, or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate. The doctrine of anticipation by inherency, among other doctrines, enforces that basic principle." See *Atlas Powder Co. v. IRECO Inc.* 51 USPQ2d 1943 (Fed. Cir. 1999).

See also, *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) The board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A US patent to Dart disclosed inoculation using *P. cepacia* bacteria for protecting the plant from fungal disease. Dart was silent with regard to nematode inhibition, but the Board concluded that nematode

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inhibition was an inherent property of the bacteria, and therefore of the method as disclosed by Dart.

Thus, a reference may be anticipatory if it discloses every limitation of the claimed invention either explicitly or inherently. A reference includes an inherent characteristic if that characteristic is the "natural result" flowing from the reference's explicitly explicated limitations. Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

In the instant case, the effect on NO synthetase flows from the administration of a known antagonist. Thus applicants are incorrect in arguing that the anticipatory rejection is improper.

Claims 1, 5, 9-11 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Thiemermann *et al.* [U].

The claims are directed to a one step method of intravenously administering from 20-500 µg/kg of a peptide, oligopeptide or protein, containing an arginine available to NOS, to a mammal in order to regulate NO production.

Thiemermann *et al.* disclose administration of 1-30mg/kg of NO<sub>2</sub>-Arg-L-arginine and other dipeptides containing arginine, *in vivo*, to rats raises blood pressure (vasoconstrictors). This is the same one step method as claimed.

#### *Response to Arguments*

Applicants argue that at the time of applicants' invention one of skill in the art would not have realized from the teachings of Thiererman et al. that the administration of the dipeptides of Thiererman et al. would result in stimulating or inhibiting NO production.

A reference may be anticipatory if it discloses every limitation of the claimed invention either explicitly or inherently. A reference includes an inherent characteristic if that characteristic is the "natural result" flowing from the reference's explicitly explicated limitations. Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Under the principles of inherency, if the prior art necessarily functions in

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accordance with, or includes, the claimed limitations, it anticipates. See *In re King*, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. See *Titanium Metals*, 778 F.2d at 780. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. See *id.* at 782.

In the instant case, the effect on NO synthetase flows from the administration of a known antagonist. Thus applicants are incorrect in arguing that the anticipatory rejection is improper.

Claims 1, 3, 5, 6, 9-11, 15 and 16 remain rejected under 35 U.S.C. 102(b) as being anticipated by US 4585757 [A].

US 458575 discloses the administration of arginine containing peptides, CIP fragment, contraceptive tetrapeptide and bradykinin in the range of 50-500 µg/kg to lower blood pressure (Table 2 and 3).

#### *Response to Arguments*

Applicants continue to argue that one of skill in the art would not appreciate the effects of the administration of the arginine-containing peptides of '757. The rebuttal of this argument concerning the knowledge of one of skill in the art is above and is not repeated.

Applicants argue that the reference does not demonstrate the administration of any of the peptides of claim 16. This is incorrect. See the reference at Table 2.

Claims 1, 3, 5, 6, 9-11, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by US 6143719 [A].

US 6143719 discloses the intravenous administration in rabbits of Seq ID # 19 which is the same sequence as applicants' Seq. Id. # 5 in example III, col. 19-20. Although the reference is silent with regard to the effect of the peptide on NOS, as the recipient, compound administered, mode of administration and amounts are the same, the result would inherently be the same as the claimed result.

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*Claim Rejections – 35 USC § 103*

Claims 1, 3, 5, 6, 9-11, 13, 15, and 16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 4152425 [B].

US 4152425 discloses the infusion of 10-3000 $\mu$ g of kinin/I solution. The specifically preferred kinin is bradykinin. The infusion amount is exemplified at one liter (col. 5, l. 18).

The use of up to 3000 $\mu$ g/I/80kg = 37.5 $\mu$ g bradykinin/kg in the method of US '425 would have been obvious because this is within the range of administration of bradykinin taught in the reference.

Claims 1, 5, 6, 9-11, 15, and 16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5648333 [C].

US 5648333 discloses the administration of the various peptides which are bradykinin antagonists in the range of 10 $\mu$ g-10mg/kg (Col. 18, l. 25 and Table 1).

Although the references are silent with regard to the effects of the administration of bradykinin or arginine containing peptides on NO production, it is reasonable to assume that the effects would be the same as claimed because, the patient is the same, the compounds administered are the same, the dosage is the same, the mode of administration is the same; therefore, the results would inherently be the same.

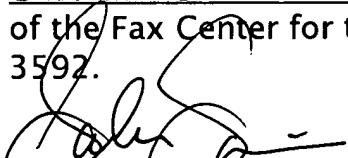
*Response to Arguments*

Applicants argue that their claims are patentable because they allege that others have been granted multiple patents for the same one step administration of a drug. First, as counsel well knows, the examiner cannot comment on issued patents and each case is examined on its own merits. Applicants would better further their case by amending the claims to avoid the prior art by either distinguishing the recipient of the peptides from the prior art recipients, distinguishing the compounds to be administered (for example, canceling the limitations directed to BK, BK fragment 1-5 and the non-examined poly-arginine or L-arginine) or distinguishing the concentration or modes of administration of the compounds from the prior art disclosures; applicant has done none of the above. Thus, the rejections remain.

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To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1651. The supervisor for 1651 is M. Wityshyn, (703) 308-4743. The normal work schedule for Examiner Saucier is 8:30AM to 6:00PM Tuesday-Friday and every other Monday.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (703) 308-1084. Status inquiries must be directed to the Customer Service Desk at (703) 308-0197 or (703)-308-0198. The number of the Fax Center for the faxing of papers is (703) 308-2742 or (703) 305-3592.



Sandra Saucier  
Primary Examiner  
Art Unit 1651  
December 13, 2001